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A new synthesis of spiro-fused 1,4-benzothiazines

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A new preparative procedure was developed for the synthesis of spiro-fused 1,4-benzothiazines by thermal heterocyclization of *S*-benzyl and *S*-phenacyl derivatives of *o*-indothiophenol.

Key words: *o*-indothiophenol, benzothiazine.

ortho-Substituted quinone *N*-arylimines[1,2] are promising chelating ligands[3] and starting compounds for the preparation of previously unknown spiro-fused benzoazines.[4] However, mercapto-substituted quinone *N*-arylimines have been previously inaccessible because of the formation of S—S dimers under the standard conditions of condensation of *o*-aminothiophenol with quinones acting as oxidants.

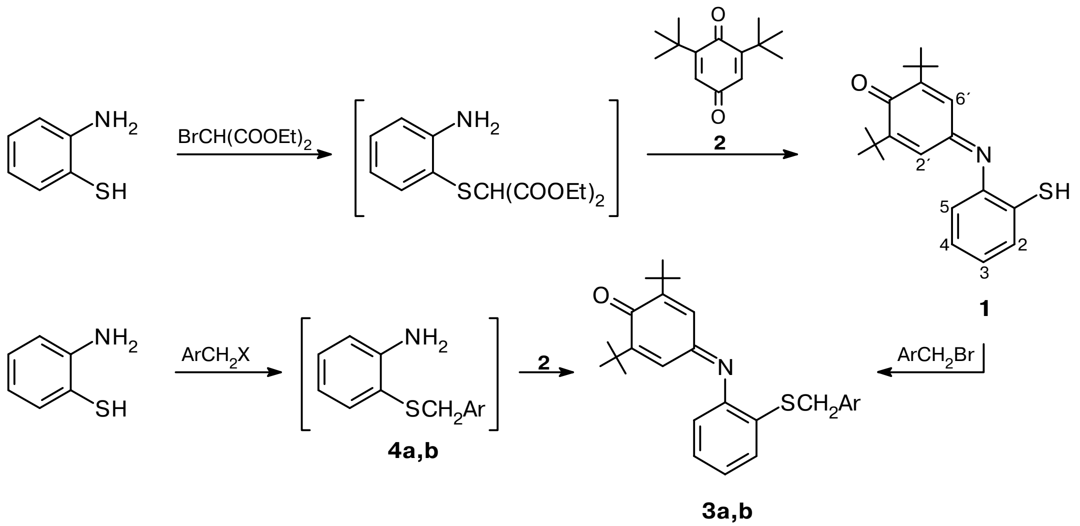
Results and Discussion

We succeeded in preparing *o*-indothiophenol (**1**) from *o*-aminobenzenethiol with the use of diethyl malonate as the SH-protective group, which has previously been unknown in the traditional chemistry of thiols.[5] The resulting sulfide was treated without isolation with 2,6-di-*tert*-butyl-1,4-benzoquinone (**2**) in MeOH to obtain the target compound **1** in 58% yield (Scheme 1).

The present study was aimed at employing intramolecular heterocyclization of *S*-methylene derivatives of *o*-indothiophenol for the synthesis of previously inaccessible spiro-fused benzothiazines. The starting quinone *N*-(*o*-benzylthio)phenylimines (**3**) were prepared (see Scheme 1) by either condensation of *o*-aminophenyl benzyl sulfides (**4**) with benzoquinone **2** (method *A*) or alkylation of *o*-indothiophenol (**1**) with benzyl halides (method *B*). The method *A* is advantageous because of its simplicity, higher yields of the target products, and the possibility of performing the one-pot synthesis.

However, the corresponding phenacyl sulfides cannot be prepared according to the method *A* because the reaction of *o*-aminobenzenethiol with *p*-bromophenacyl

Scheme 1



Ar = Ph (**a**), 4-$NO_2C_6H_4$ (**b**); X = Cl, Br

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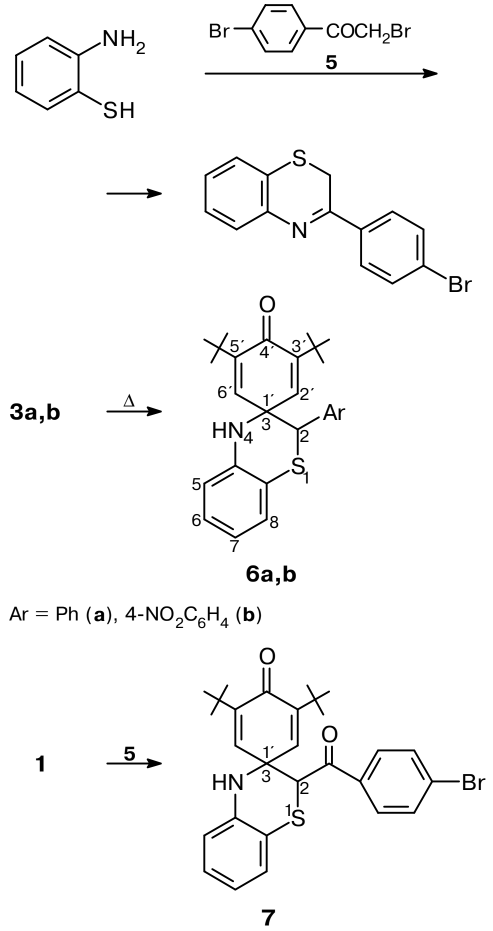
bromide (**5**) is known[6] to afford directly 3-*p*-bromophenyl-2*H*-1,4-benzothiazine (Scheme 2).

Scheme 2



Like analogous *o*-indophenol derivatives,[4] sulfides **3** are converted into spirobenzothiazines **6** upon heating (see Scheme 2). However, intramolecular cyclization of the thio analogs proceeds much more rapidly. Benzyl sulfide **3a** undergoes cyclization on refluxing in toluene, whereas cyclization of 4-nitrobenzyl sulfide **3b** proceeds even on refluxing in benzene. The formation of spirobenzothiazines **6** from sulfides **3** is evidenced by the appearance of two one-proton signals of the CH and NH groups instead of the two-proton signal of the methylene group. The reaction of *o*-indothiophenol (**1**) with phenacyl bromide **5** gave rise directly to spirobenzothiazine **7** (see Scheme 2). Its structure was confirmed by the fact that the signals for two *tert*-butyl groups and two protons of the cyclohexadiene ring are isochronous and also by the presence of one-proton singlet signals for the protons of the CH and NH groups.

The spirane structure of benzothiazine **6b** was unambiguously established by X-ray diffraction analysis (Fig. 1, Tables 1 and 2).

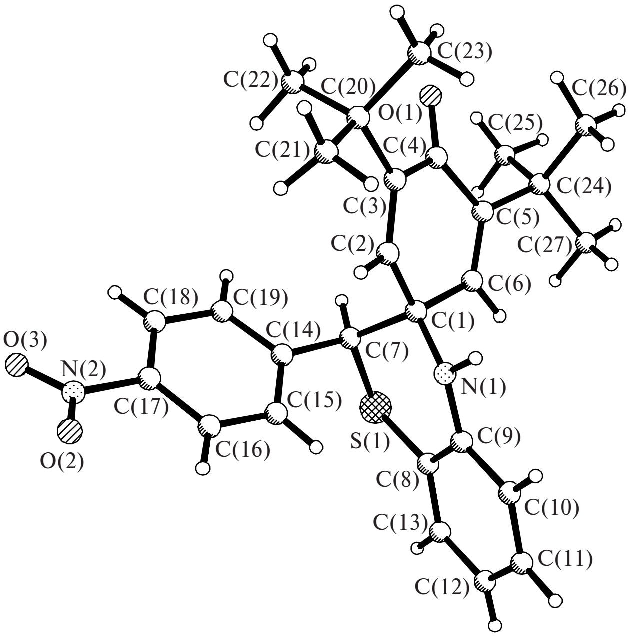


Fig. 1. Structure of molecule **6b**.

Table 1. Principal bond lengths (*d*) in molecule **6b**

Bond	*d*/Å	Bond	*d*/Å
S(1)—C(8)	1.762(2)	C(3)—C(4)	1.496(3)
S(1)—C(7)	1.821(2)	C(3)—C(20)	1.532(3)
N(1)—C(9)	1.392(3)	C(4)—C(5)	1.485(3)
N(1)—C(1)	1.458(3)	C(5)—C(6)	1.334(3)
N(2)—O(3)	1.215(3)	C(5)—C(24)	1.548(3)
N(2)—O(2)	1.231(3)	C(7)—C(14)	1.502(3)
N(2)—C(17)	1.458(3)	C(8)—C(13)	1.396(3)
O(1)—C(4)	1.229(2)	C(8)—C(9)	1.407(3)
C(1)—C(2)	1.493(3)	C(9)—C(10)	1.398(3)
C(1)—C(6)	1.509(3)	C(10)—C(11)	1.372(4)
C(1)—C(7)	1.565(3)	C(11)—C(12)	1.389(4)
C(2)—C(3)	1.338(3)	C(12)—C(13)	1.382(4)

Table 2. Principal bond angles (ω) in molecule **6b**

Angle	ω/deg	Angle	ω/deg
C(8)—S(1)—C(7)	101.0(1)	O(1)—C(4)—C(3)	120.4(2)
C(9)—N(1)—C(1)	123.8(2)	C(5)—C(4)—C(3)	118.4(2)
O(3)—N(2)—O(2)	122.8(2)	C(6)—C(5)—C(4)	118.4(2)
O(3)—N(2)—C(17)	119.1(2)	C(6)—C(5)—C(24)	123.2(2)
O(2)—N(2)—C(17)	118.0(2)	C(4)—C(5)—C(24)	118.3(2)
N(1)—C(1)—C(2)	107.0(2)	C(5)—C(6)—C(1)	123.9(2)
N(1)—C(1)—C(6)	111.9(2)	C(14)—C(7)—C(1)	114.3(2)
C(2)—C(1)—C(6)	111.8(2)	C(14)—C(7)—S(1)	113.1(2)
N(1)—C(1)—C(7)	109.0(2)	C(1)—C(7)—S(1)	111.9(2)
C(2)—C(1)—C(7)	107.3(2)	C(13)—C(8)—S(1)	117.6(2)
C(6)—C(1)—C(7)	109.7(2)	C(9)—C(8)—S(1)	123.1(2)
C(3)—C(2)—C(1)	125.2(2)	N(1)—C(9)—C(10)	119.1(2)
C(2)—C(3)—C(4)	117.1(2)	N(1)—C(9)—C(8)	122.3(2)
C(2)—C(3)—C(20)	123.0(2)	C(19)—C(14)—C(7)	118.5(2)
C(4)—C(3)—C(20)	119.9(2)	C(15)—C(14)—C(7)	123.1(2)
O(1)—C(4)—C(5)	121.2(2)		

The six-membered C(1)...C(6) ring in the molecule **6b** adopts a boat conformation with the C(1) and C(4) atoms deviating from the plane through the remaining atoms of the ring by −0.205(4) and −0.216(4) Å, respectively. The presence of the bulky *tert*-butyl substituents causes noticeable steric strain in this fragment of the molecule, which is manifested in the following shortened intramolecular contacts: C(2)...H(21A), 2.77(3) Å (the sum of the van der Waals radii[7] of the C and H atoms is 2.87 Å); C(2)...H(21B), 2.80(3) Å; H(2)...C(14), 2.73(2) Å; H(2)...C(21), 2.45(2) Å; H(2)...H(21A), 2.28(3) Å (the sum of the van der Waals radii[7] of the H atoms is 2.32 Å); H(2)...H(21B), 2.23(3) Å; C(4)...H(23A), 2.74(3) Å; C(4)...H(26C), 2.77(4) Å; C(6)...H(27B), 2.85(4) Å; H(6)...C(27), 2.47(2) Å; and H(6)...H(27A), 2.31(3) Å. In addition, the C(3)—C(20) and C(5)—C(24) bonds are elongated to 1.532(3) and 1.548(3) Å, respectively, compared to the average C(sp^2)—C(sp^3) bond length (1.507 Å).[8]

The O(1) atom of the carbonyl group forms two intermolecular C—H...O hydrogen bonds with the H atoms of the aryl rings: H(12)...O(1′) (0.5 − *y*, *x*, 0.5 − *z*), 2.66(3) Å; C(12)...O(1′), 3.522(4) Å; the C(12)—H(12)...O(1′) angle is 151(2)°, and H(16)...O(1″) (*x*, *y*, *z* − 1), 2.41(2) Å; C(16)...O(1″), 3.304(3) Å; the C(16)—H(16)...O(1″) angle is 153(2)°.

The six-membered heterocycle adopts a half-chair conformation with the C(1) and C(7) atoms deviating from the plane through the remaining atoms of the ring by −0.337(4) and 0.418(3) Å, respectively. The aryl substituent at the C(7) atom is in the axial position (the C(8)—S(1)—C(7)—C(14) torsion angle is −86.7(2)°) and is substantially rotated with respect to the C(7)—S(1) bond (the S(1)—C(7)—C(14)—C(15) torsion angle is 65.2(3)°). Such position of the substituent gives rise to the shortened intramolecular contacts: H(7)...H(19), 2.26(3) Å; N(1)...C(15), 3.097(3) Å (the sum of the van der Waals radii[7] of the C and N atoms is 3.21 Å); C(8)...H(15), 2.80(2) Å; and C(9)...H(15), 2.71(2) Å.

The nitro group in the molecule **6b** is rotated with respect to the plane of the benzene ring (the O(2)—N(2)—C(17)—C(16) torsion angle is 22.9(4)°). The H(1) atom forms a bifurcated intermolecular hydrogen bond with the O atoms of the nitro group: H(1)...O(2‴) (*y* − 0.5, 1 − *x*, 0.5 + *z*), 2.22(3) Å; N(1)...O(2‴), 3.077(3) Å; the N(1)—H(1)...O(2‴) angle is 173(2)°; and H(1)...O(3‴), 2.64(2) Å; N(1)...O(3‴), 3.224(3) Å; the N(1)—H(1)...O(3‴) angle is 127(2)°. In addition, the O(3) atom is involved in the formation of the intermolecular C—H...O hydrogen bond: H(18)...O(3⁗) (−*x* + 1, −*y* + 1, −*z*), 2.55(3) Å; C(18)...O(3⁗), 3.187(4) Å; the C(18)—H(18)...O(3⁗) angle is 127(2)°.

Experimental

The ^1H NMR spectra were recorded on a Bruker DPX-250 spectrometer (250 MHz) at 25 °C ($CDCl_3$) with Me_4Si as the internal standard.

***o*-Indothiophenol (1).** A solution of *o*-aminobenzenethiol (0.02 mol) in MeOH (15 mL) was added to a solution of KOH (0.02 mol) in MeOH (15 mL) and the reaction mixture was stirred for 0.5 h. Then a solution of diethyl bromomalonate (0.02 mol) in MeOH (15 mL) was added. The reaction mixture was brought to boiling and kept at ~20 °C for 1 h. Then benzoquinone **2** (0.02 mol) was added. The mixture was refluxed for 15 h and cooled. The precipitate that formed was filtered off, purified by column chromatography (Al_2O_3, benzene—light petroleum, 1 : 2), and recrystallized from MeOH. The yield was 58%, m.p. 58 °C. Found (%): C, 73.35; H, 7.69; N, 4.28. $C_{20}H_{25}NOS$. Calculated (%): C, 73.48, H, 7.55, N, 4.39. ^1H NMR, δ: 1.20 and 1.33 (both s, 9 H each, Bu^t); 6.65 (d, 1 H, H(2), *J* = 7.4 Hz); 6.77 and 7.09 (both d, 1 H each, H(2′), H(6′), *J* = 2.4 Hz); 7.10—7.22 (m, 2 H, H(3), H(4)); 7.34 (s, 1 H, SH); 7.67 (d, 1 H, H(5), *J* = 7.4 Hz).

3,5-Di-*tert*-butyl-*p*-benzoquinone *N*-(*o*-benzylthio)phenylimine (3a). ***A.*** A solution of *o*-aminobenzenethiol (0.02 mol) in MeOH (15 mL) was added to a solution of KOH (0.02 mol) in MeOH (15 mL). The reaction mixture was stirred for 0.5 h and a solution of benzyl chloride (0.02 mol) in MeOH (15 mL) was added. The reaction mixture was brought to boiling and kept at ~20 °C for 1 h. Then benzoquinone **2** (0.02 mol) was added and the mixture was refluxed for 5 h. The solvent was evaporated, the residue was purified by column chromatography (Al_2O_3, benzene—light petroleum, 1 : 2), and compound **3a** was obtained in 80% yield, m.p. 98—100 °C (from MeOH).

B. *o*-Indothiophenol **1** (0.02 mol) was added to a solution of KOH (0.02 mol) in MeOH (35 mL) and the reaction mixture was stirred with gentle heating until the precipitate completely dissolved. Then benzyl chloride (0.02 mol) was added and the reaction mixture was refluxed for 5 h. The product was isolated as described above, the yield was 35%.

Found (%): C, 77.75; H, 7.39; N, 3.45. $C_{27}H_{31}NOS$. Calculated (%): C, 77.65; H, 7.48; N, 3.35. ^1H NMR, δ: 1.18 and 1.31 (both s, 9 H each, Bu^t); 4.10 (s, 2 H, CH_2); 6.63 (d, 1 H, H(2), *J* = 7.4 Hz); 6.70 and 7.08 (both d, 1 H each, H(2′), H(6′), *J* = 2.5 Hz); 7.10—7.35 (m, 8 H, H(3), H(4), H(5), Ph).

3,5-Di-*tert*-butyl-*p*-benzoquinone *N*-[*o*-(4-nitrobenzylthio)]phenylimine (3b). ***A.*** *o*-Aminobenzenethiol (0.02 mol) was alkylated with *p*-nitrobenzyl bromide in MeOH in the presence of KOH analogously to the synthesis of **3a**. The reaction with benzoquinone **2** lasted for 4 h. After column chromatography (Al_2O_3, benzene—light petroleum, 1 : 2), compound **3b** was obtained in 76% yield, m.p. 153 °C.

B. Alkylation of *o*-indothiophenol **1** (0.02 mol) with *p*-nitrobenzyl bromide in MeOH in the presence of KOH was carried out as described for **3a**. The yield was 30%. Found (%): C, 70.31; H, 6.43; N, 6.18. $C_{27}H_{30}N_2O_3S$. Calculated (%): C, 70.10; H, 6.54; N, 6.06. ^1H NMR, δ: 1.17 and 1.32 (both s, 9 H each, Bu^t); 4.13 (s, 2 H, CH_2); 6.65 and 7.06 (both d, 1 H each, H(2′), H(6′), *J* = 2.4 Hz); 6.66 (d, 1 H, H(2), *J* = 6.8 Hz); 7.08—7.26 (m, 3 H, H(3), H(4), H(5)); 7.44 and 8.11 (both d, 2 H each, H(2″), H(6″), H(3″), H(5″), *J* = 8.7 Hz).

3′,5′-Di-*tert*-butyl-4′-oxo-2-phenyl-2,3-dihydrospiro(4*H*-1,4-benzothiazine-3,1′-cyclohexa-2′,5′-diene) (6a). A solution of sulfide **3a** (0.005 mol) in toluene (15 mL) was refluxed for 5 h and concentrated. Then the residue was purified by column chromatography (Al_2O_3, benzene). The product was dried and triturated with light petroleum until the crystalline precipitate formed. The yield was 78%, m.p. 175 °C. Found (%): C, 77.81; H, 7.44; N, 3.39. $C_{27}H_{31}NOS$. Calculated (%): C, 77.65; H, 7.48; N, 3.35. ^1H NMR, δ: 1.02 and 1.14 (both s, 9 H each, Bu^t); 4.17 (s, 1 H, NH); 4.39 (s, 1 H, H(2)); 6.39 and 6.89 (both d, 1 H each, H(2′), H(6′), *J* = 3.0 Hz); 6.62 (d, 1 H, H(8), J = 8.0 Hz); 6.72 (dd, 1 H, H(7), J = 7.3 and 8.0 Hz); 6.99 (dd, 1 H, H(6), J = 7.3 and 7.9 Hz); 7.10—7.22 (m, 6 H, H(5), Ph).

3′,5′-Di-*tert*-butyl-4′-oxo-2-(*p*-nitrophenyl)-2,3-dihydrospiro(4*H*-1,4-benzothiazine-3,1′-cyclohexa-2′,5′-diene) (6b). A solution of sulfide **3b** (0.005 mol) in benzene (15 mL) was refluxed for 0.5 h. The solvent was evaporated and the residue was purified by column chromatography (Al_2O_3, benzene). The yield was 88%, m.p. 202 °C (from benzene). Found (%): C, 70.26; H, 6.45; N, 6.14. $C_{27}H_{30}N_2O_3S$. Calculated (%): C, 70.10; H, 6.54; N, 6.06. ^{1}H NMR, δ: 1.04 and 1.13 (both s, 9 H each, Bu^t); 4.21 (s, 1 H, NH); 4.38 (s, 1 H, H(2)); 6.48 and 6.67 (both d, 1 H each, H(2′), H(6′), J = 3.0 Hz); 6.65 (d, 1 H, H(8), J = 7.5 Hz); 6.79 (dd, 1 H, H(7), J = 7.5 and 8.7 Hz); 7.03 (dd, 1 H, H(6), J = 8.7 and 7.8 Hz); 7.12 (d, 1 H, H(5), J = 7.8 Hz); 7.32 and 8.08 (both d, 2 H each, H(2″), H(6″), H(3″), H(5″), J = 8.8 Hz).

2-*p*-Bromobenzoyl-3′,5′-di-*tert*-butyl-4′-oxo-2,3-dihydrospiro(4*H*-1,4-benzothiazine-3,1′-cyclohexa-2′,5′-diene) (7). *o*-Indothiophenol **1** (0.02 mol) was added to a solution of KOH (0.02 mol) in MeOH (35 mL) and the reaction mixture was stirred with gentle heating until thiophenol **1** completely dissolved. Then a solution of *p*-bromophenacyl bromide **5** (0.02 mol) in MeOH (20 mL) was added and the mixture was refluxed for 3 h. The solvent was evaporated and the residue was purified by column chromatography (Al_2O_3, benzene—light petroleum, 1 : 1). The yield was 28%, m.p. 200 °C. Found (%): C, 75.38; H, 7.13; N, 3.28. $C_{28}H_{31}NO_2S$. Calculated (%): C, 75.47; H, 7.01; N, 3.14. ^{1}H NMR, δ: 1.40 (s, 18 H, Bu^t); 5.37 (s, 1 H, NH); 6.00 (d, 1 H, H(8), J = 7.8 Hz); 6.70—6.88 (m, 3 H, H(5), H(6), H(7)); 6.89 (s, 1 H, H(2)); 7.01 (s, 2 H, H(2′), H(6′)); 7.42 and 7.49 (both d, 2 H each, H(3″), H(5″), H(2″), H(6″), J = 8.6 Hz).

X-ray diffraction study of compound 6b. Crystals of $C_{27}H_{30}O_3N_2S$ are tetragonal, at 138(2) K, a = 22.015(8) Å, c = 10.697(6) Å, V = 5184(4) Å^3, crystal dimensions are 0.5×0.3×0.2 mm, space group $P4_2/n$, Z = 8, d_{calc} = 1.185 g cm^{-3}, $F(000)$ = 1968, μ = 0.154 mm^{-1}.

The intensities of 5953 reflections (of which 5657 reflections were independent, R_{int} = 0.068) were measured on an automated four-circle Siemens P3/PC diffractometer (graphite monochromator, Mo-Kα radiation, ω/2θ scanning technique, $2\theta_{\max}$ = 54°).

The structure was solved by the direct method using the SHELXTL PLUS program package.[9] The positions of all H atoms were revealed from the difference electron density synthesis. The anisotropic (isotropic for the H atoms) refinement by the full-matrix least-squares method (418 parameters) based on F^2 using 5600 reflections converged to R_1 = 0.044 (for 2515 reflections with $F > 4\sigma(F)$), wR_2 = 0.116, S = 0.82. The atomic coordinates for the structure of **6b** and the complete tables of the bond lengths and bond angles were deposited with the Cambridge Structural Database. The principal bond lengths and bond angles are listed in Tables 1 and 2, respectively.

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